20 Evidence for noradrenaline-mediated changes in platelet and heart function following chronic treatment of rats and guinea pigs with nicotine

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Introduction: Platelets of rats chronically pretreated for 8 weeks with nicotine (10mg/kg/day, applied from subcutaneously implanted osmotic minipumps) exhibited reduced sensitivity towards the aggregatory stimulant ADP [Becker et al. (1988) Klin Wochenschr 66 (Suppl XI),28 - 36]. This action of nicotine could be prevented by simultaneously applying the ß-blocker propranolol, was not mimicked by adrenaline, and was not elicited in guinea pigs, a species known to lack thrombocytic adrenoceptors. A species specific effect of nicotine was also found when hearts isolated from pretreated animals performed pressure-volume work under standardized conditions [Becker and Gerlach (1988) in: Rand and Thurau (eds) The pharmacology of nicotine. IRL Press, Oxford, pp 140]. Hearts of guinea pigs exhibited a transitory reduction in performance after 1 - 2 weeks of nicotine application, whilst longer periods of pretreatment (8 - 12 weeks) improved heart function vs controls. No such effects were noted for the rat.

Problem and Approach: To establish whether the described actions of nicotine were due to a selective, chronic elevation of the noradrenergic tone, platelet function was assessed in rats chronically treated with noradrenaline (0.05 and 0.5 mg/kg/day for 8 weeks). In other sets of experiments, the density of ß-adrenoceptors was determined in hearts of guinea pigs and rats after various periods of nicotine application. Moreover, the myocardial tissue levels of high energy phosphates (ATP, CrP) were measured following isolation of pretreated guinea pig hearts to ascertain the degree of metabolic stress.

Results: i) Chronic application of noradrenaline to rats blunted platelet responsiveness towards ADP to the same extent as did nicotine. ii) The ß-adrenoceptor density of rat hearts declined rapidly (-50% after 1 week of nicotine), but then remained constant. Since only the density of control hearts showed a very strong, growth-dependent drop, densities of controls and nicotine treated hearts were about the same again after 8 weeks, albeit at a lower level. In contrast, ß-adrenoceptor density in hearts of guinea pigs fell more slowly during nicotine application; there was no reduction relative to controls after 1 week, however a 40 to 50% decline had developed after 4 and 8 weeks. iii) In hearts treated for 2 weeks with nicotine, ATP levels and work performance proved to be lower than in controls by about 10% and 20%, respectively, but there was no difference after 6 weeks.

Conclusions: Chronic application of nicotine to rats and guinea pigs seems to generally enhance ß-adrenoceptor mediated effects by elevating noradrenaline levels. In rats this leads to a reduction in blood platelet activity. However, the rat heart is protected from any untoward metabolic stress due to rapid down-regulation of ß-adrenoceptor density. Since the down-regulation proceeds more slowly in the guinea pig, it may be assumed that full sympathetic stimulation of the heart is still possible after about 2 weeks of treatment, cardioprotection only becoming manifest after about 4 weeks of nicotine application. **In summary,** effects of nicotine clearly vary with the animal species, the organ or cell type, and the duration of chronic application.

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